REMARKS

Claims 1-22 are pending in this application. Claim 11 has been canceled. Claims 1, 3, 4, 10, 18, and 22 have been amended. No new matter has been added. After entry of the amendments, Claims 1-10 and 12-22 will be pending in the application.

Supplemental Information Disclosure Statement

Applicants have attached an Supplemental Information Disclosure Statement that lists the full-length articles in the abstracts cited in the Office Action.

Amendment to the Specification

The specification has been amended to add the terms "cocaine addiction" and "pain", as recited in original claims 14 and 19, respectively. It is well-established that the specification may be amended with the subject mater of the claims, since claims are considered part of the disclosure. MPEP § 2163.06. Therefore, Applicants respectfully request entry of the amendment.

Claim Rejection – 35 U.S.C. 112, first paragraph

Claims 4, 10, and 22 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to enable the scope of the claims. Claims 4 and 22 are independent claims directed to methods of treating central nervous system (CNS) disorders and methods of enhancing cognition, respectively. Claim 10 depends from claim 4 and recites a neurodegenerative disorder as a specific CNS disorder treatable by the method of claim 4. While the Action only formally rejects these three claims, Applicants note that the Action later goes on to state that methods of treating of certain specific CNS disorders as recited in some of the dependent claims, are also not enabled. The Applicants' arguments herein apply also to these assertions of non-enablement, as well as to the formal rejections of claims 4, 10, and 22.

The Action concedes that a number of specific disorders, as recited in the dependent claims, are enabled. The Action, however, alleges that the specification does not enable methods of treating all disorders of the CNS, all neurodegenerative disorders, all forms of pain, and all forms of urinary incontinence. Further, the Action disagrees that the specification enables the claims drawn to method of treating certain specific disorders, such as amnesia, Shy Drager Syndrome, borderline personality disorder, late luteal phase dysphoric disorder, Gilles de la Tourette Syndrome, vasomotor flushing, and chronic fatigue syndrome.

After analyzing the various factors presented in *in re Wands*, the Action asserts that a person of skill in the art would have to engage in undue experimentation to "test which central nervous system diseases can be treated by the compound encompassed in the instant claims, with no assurance of success." (Office Action, page 7). While Applicants believe that one of skill in the art would not have to engage in undue experimentation to determine which CNS disorders can be treated by the claimed compounds, Applicants have amended claim 4 to recite those CNS disorders disclosed in the specification. Similarly, Applicants have amended claim 10 to recite the specific neurodegenerative disorders cited in claim 11. With regard to the methods of treating other disorders alleged to be non-enabled in the Action, Applicants respectfully disagree that the Office has carried its burden under § 112.

35 U.S.C. § 112, first paragraph, has been interpreted to require that a claimed invention be enabled so that a one of skill in the art can make and use the invention without undue experimentation. In making a § 112 rejection based upon non-enablement, the Office has the initial burden to establish "a reasonable basis to question the enablement provided for the claimed invention." MPEP 2164.04. The MPEP goes on to state:

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

MPEP 2164.04. Hence, the burden falls squarely upon the Office to not only assert "*why* it doubts the truth or accuracy of any statement in a supporting disclosure", but "to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *in re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). Applicants respectfully assert that the explanations and evidence produced by the Office do not establish a lack of enablement under § 112 for the specific CNS disorders cited in the amended claims.

In supporting its conclusion that that undue experimentation would be required to practice the methods of the invention, the Action points to state of the art (as summarized in several abstracts) and alleges a lack of predictability in the art, a lack of direction or guidance, an absence of working examples, a large quantity of experimentation needed, and a wide claim breadth. These explanations, however fail to support adequately the Action's assertion of undue experimentation.

The *in re Wands* factors asserted by the Action do not provide sufficient evidence to meet the Office's burden under § 112. For example, the Action points to the absence of working examples, stating that there is no pharmacological data in the specification regarding the use of the claimed compounds to treat the claimed diseases. The Action fails to recognize that the compounds of the current invention are prodrugs of a known metabolite of venlafaxine with known ability to modify the serotonin receptors of the central nervous system and to treat a multitude of CNS disorders. One of ordinary skill in the art would recognize that prodrugs are simply a novel way of delivering a drug to the patient *in vivo*. Hence, the knowledge in the art regarding methods of treating CNS disorders with venlafaxine is equally applicable to the prodrugs of the invention and does not need to be explicitly provided in the specification. As stated in MPEP § 2164.03, the more that is known in the art about how to make and use the invention, the "less information needs to be explicitly stated in the specification." In fact, it is

preferable if this information is omitted from the specification. MPEP § 2164.01. Given the knowledge in the art about the efficacy of venlafaxine in treating CNS disorders, Applicants respectfully assert that the lack of examples in the specification does not make this factor weigh against enablement, particularly given the admitted high level of skill in the art.

Similarly, the Action asserts that there is little direction or guidance in the specification given the lack of "experimental assays" disclosed. Again, Applicants respectfully reiterate that the instant compounds are prodrugs of a metabolite of a known pharmacological agent, the efficacy of which is disclosed in the art. Accordingly, Applicants respectfully assert that those of skill in the art would be enabled to use the claimed prodrugs for the uses established for the known pharmacological agent.

Additionally, the Action maintains that the methods of the invention are "highly unpredictable" based upon its general assertions about the nature of the pharmaceutical arts, which would prevent "one of ordinary skill in the art from accepting any therapeutic regimen on its face". Applicants respectfully assert that one of ordinary skill in the art is not being forced to accept anything on its face given the knowledge in the art regarding venlafaxine in treating CNS disorders. The Action's generalized assertion regarding the nature of pharmaceutical arts at large is inapplicable to the specific methods being claimed here. Indeed, one of ordinary skill practicing in the pharmaceutical arts recognizes highly predictable results when comparing a prodrug to the active agent it forms *in vivo*.

Further, the references cited by the Action in support of its assertions of unpredictability do not render the methods non-enabled. If anything, these references actually provide affirmative support for enablement, rather than helping the Office establish its initial burden to provide objective reasons for doubting the efficacy of the claimed methods. For example, the Action, at page 4, cites Hcaplus 129:239318 (D. Nutt, et al., Reviews in Contemporary Pharmacotherapy (1998), 9(5), 321-331), stating "evidence...is relatively scanty at the present

time as to whether venlafaxine has a role in the management of chronic fatigue syndrome." In point of fact, the full-length article reveals that venlafaxine has been used successfully to treat patients with chronic fatigue syndrome. *Id.* at 324. Thus, despite the Action's characterization of the Nutt reference, a careful reading will show that venlafaxine is known to be effective in treating chronic fatigue disorder. Thus, the claimed prodrugs of venlafaxine would also be effective in treating chronic fatigue syndrome.

Similarly, the Action, at page 4, cites PubMed ID:16034979 (T. Saarto, et al., Cochrane Database of Systematic Reviews (2005), 3), stating "[t]here has been insufficient data for an assessment of the evidence of effectiveness of venlafaxine on some types of neuropathic pain." In point of fact, the full-length article cites two separate studies where patients were successfully treated for neuropathic pain (Simpson 2001 and Tasmuth 2002 study in appendix). If anything, this points to the efficacy of venlafaxine to treat neuropathic pain. It certainly does not provide any support for the Office's position that venlafaxine is ineffective for treating neuropathic pain.

The Action, at page 4, also cites PubMed ID:15162896 (D.R. Grothe, et al., "Treatment of Pain Syndromes with Venlafaxine," Pharmacotherapy (2004), 24(5), 621-29), stating "[a]dditional randomized, controlled trials are necessary to fully elucidate the role of venlafaxine in the treatment of chronic pain." Once again, the full-length article chronicles the effectiveness of venlafaxine for treating chronic pain, rather than demonstrating its ineffectiveness. For example, the authors note that venlafaxine has been found to be effective in several animal models of pain (p. 623) and point to various successful clinical trials using venlafaxine to treat chronic pain (p. 624-625), neuropathic pain (p. 624-626), and headaches, migraines, fibromyalgia, and postmastectomy pain syndrome (p. 626-627). The article also describes an increase in pain thresholds for trials involving human volunteers, which suggests the general use of venlafaxine to treat pain (p. 623). This article, although cited in support of the Action's enablement rejection, provides ample support for the use of venlafaxine to treat various forms of

pain. Thus, the reference supports the use of venlafaxine and, consequently, prodrugs thereof, in the treatment of pain.

The Action also points out that "currently, no antidepressants, including venlafaxine, are approved for the treatment of chronic pain syndromes" and states that venlafaxine "has adverse physiological affects." Applicants respectfully note that the criteria for attaining FDA approval of a drug are quite different than those used to determine enablement. See MPEP § 2164.05, citing *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994). Further, it is well-established that safety concerns are the province of other government agencies, rather than the USPTO. MPEP §§ 2164.05, 2107.03. Applicants respectfully submit that neither the lack of FDA approval nor the presence of adverse side-effects for a drug have any bearing on a determination with regard to enablement.

Applicants further note that the underlying articles for the abstracts cited by the Action also support enablement for some of the specific methods rejected in the Action, including late luteal dysphoric disorder (also known as premenstrual syndrome), borderline personality disorder, urinary incontinence, pain, and chronic fatigue syndrome. For example, use of venlafaxine resulted in a fall in premenstrual syndrome symptoms. D. Nutt, et al., Reviews in Contemporary Pharmacotherapy (1998), 9(5), 321, at p. 328 (abstract cited at page 4, Hcaplus 129:239318). Also, serotonergic agents have been shown to be effective in treating late luteal phase dysphoric disorder (also known as premenstrual dysphoric disorder, or PMDD). A.F. Schatzberg, "New Indications for Antidepressants," J. Clin. Psychiatry (2000), 61, 9-17, at p. 13 (abstract cited at page 3, Hacplus 134:65678). Venlafaxine is an example of a serotonergic drug. *Id.* at 9. Further, venlafaxine was used in two studies to treat borderline personality disorder. A.F. Schatzberg, "New Indications for Antidepressants," J. Clin. Psychiatry (2000), 61, 9-17, at p. 14 (abstract cited at page 3, Hacplus 134:65678). Regulators of the serotonin receptors have also have been identified as having efficacy in treating urinary incontinence.

K.B. Thor, "Targeting Serotonin and Norepinephrine Receptors in Stress Urinary Incontinence," International Journal of Gynecology and Obstetrics (2004), 86 Suppl. 1, S38-S52, at S50 (abstract cited, Hacaplus, 142:16872). This suggests that a serotonin receptor modulator like venlafaxine would be effective in regulating urinary incontinence. Further, Applicants have previously discussed the various references cited by the Office which provide support for enablement of the claimed methods for treating chronic fatigue syndrome and pain. Accordingly, Applicants respectfully assert that all of these methods are enabled, despite the Action's allegations to the contrary.

Further, in light of the amendment to claims 4 and 10, Applicants respectfully assert that the claim breath is finite and commensurate with the scope of protection sought. In *in re Angstadt*, the applicant had disclosed a large but finite list of transition metals for use in preparing catalysts for use in the processes of the claimed invention. 190 USPQ 214, 218 (CCPA 1976). The court concluded that that it was unnecessary for the applicant to disclose a test of every species covered by the claim given the finite nature of the list. *Id.* It would be routine experimentation for one of ordinary skill to simply choose a species from that finite list and test its efficacy in the process. *Id.* In the court's view, § 112 did not require that the applicant provide one of ordinary skill with absolute certainty regarding the efficacy of each and every catalyst in the claimed processes. *Id.* at 219. To do so would render "*all* 'experimentation'... 'undue,' since the term "experimentation" implies that the success of the particular activity is *uncertain.*" *Id.*

Applicants respectfully assert that it would not be a matter of undue experimentation for one of ordinary skill to practice the methods disclosed in claims 4 and 10. As amended, claims 4 and 10 disclose methods for treating a finite number of disorders. As in *in re Angstadt*, Applicants respectfully submit determination of the efficacy of the prodrug in the claimed methods would not constitute undue experimentation, given the finite number of the disorders

listed in amended claims 4 and 10 and given the fact that the majority of these methods have been affirmatively proven enabled by the references cited in the Action.

Further, according to *in re Angstadt*, it is unnecessary for Applicants to provide one of ordinary skill in the art with absolute certainty regarding the efficacy of the claimed methods to treat each and every disorder recited in the finite lists of claims 4 and 10. As previously discussed, venlafaxine has known efficacy in treating different central nervous disorders, such as most of those listed in amended claims 4 and 10. As in *in re Angstadt*, it is unnecessary that Applicants' disclosure provide one of ordinary skill in the art with absolute certainty regarding the success of the claimed method to treat each and every disorder recited in claims 4 and 10, particularly given the finite number of the disorders listed therein. In fact, given the teachings of the specification and the references cited in the Action, the Office has simply not met its burden to show that one skilled in the art would not know how to make or use the claimed invention.

For all of the reasons presented herein, Applicants respectfully submit that none of the *in re Wands* factors weighs in the Office's favor, and as such, the Office has not met its initial burden to provide objective reasons to doubt the enablement of the methods disclosed in the present application. Accordingly, Applicants respectfully request that the § 112 rejections of claims 4 and 10, and the related informal rejections of the specific method claims (methods of treating amnesia, Shy-Drager Syndrome, borderline personality disorder, late luteal phase dysphoric disorder, Gilles de la Tourette Syndrome, vasomotor flushing, and chronic fatigue syndrome) be withdrawn.

The Action also rejects claim 22, directed to methods for enhancing cognition. The action alleges that "the enhancing of cognition must be related to a disease that needs to be improved and this disease needs to be recited." (Office Action, pages 2-3). Applicants respectfully assert that cognition enhancement may occur outside of and separate from treatment of any disease or disorder. Thus, the claimed method of enhancing cognition need

not be associated with any disease or disorder in order to enable those of ordinary skill in the art to use the claimed method.

The Action also alleges that claim 22 is not enabled for the reasons summarized above. Applicants respectfully reiterate that the initial burden is on the Office to show that the method of enhancing cognition is not enabled. Nonetheless, Applicants draw the Office's attention to U.S. Patent No. 5,530,013 (cited in the specification of the present invention, page 1, lines 27-28), which clearly discloses the use of venlafaxine for the inducement of cognition enhancement and which provides experimental data in support of the method's efficacy This reference clearly demonstrates that the method of claim 22 is commensurate with the scope of protection sought. No undue experimentation is required. Accordingly, Applicants respectfully assert that the requirements of 35 U.S.C. § 112, first paragraph have been met.

Withdrawal of the rejections of claims 4, 10, and 22, as well as the informal rejections of the specific method claims objected to in the Action, based on 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claim Rejections - 35 U.S.C. § 112, second paragraph

Claims 1, 2, 3, and 4-21 stand rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Independent claims 1, 3, and 4 contain the plural phrase "salts or hydrates thereof" with reference to the claimed compound. Applicants have amended the phrase to be singular in nature, in accordance with the Examiner's helpful suggestion. Applicants respectfully submit that this amendment corrects a grammatical error and is not intended to narrow the scope of the claims.

Additionally, the Action questions "what hydrates the applicant is claiming". Applicants respectfully assert that those of ordinary skill in the art will understand the meaning of "hydrates thereof." Applicants respectfully submit that those of skill in the art will recognize "hydrates" as being compounds having water in weak chemical combination. As such, the hydrates are

compounds of formula I in weak chemical combination with varying amounts of water. Applicants respectfully assert that the claim as written is clear and definite.

Claim 18 is rejected under § 112, second paragraph, as allegedly lacking antecedent basis. The Action alleges that chronic obstructive pulmonary disease is not a central nervous system disorder, and that urinary incontinence may have diverse etiologies. While they assert that one of ordinary skill in the art would recognize that both diseases are related to dysfunction of the central nervous system, Applicants have rewritten claim 18 to remove dependency on claim 4 in order to further prosecution.

Applicants respectfully assert that all requirements of 35 U.S.C. § 112 are satisfied. Withdrawal of the rejections based on 35 U.S.C. § 112 is respectfully requested.

Claim Rejections - 35 U.S.C. § 103

Claims 1-19 stand rejected under 35 U.S.C. § 103, as being allegedly obvious over U.S. Patent No. 6,441,048 (hereinafter "Jerussi '048") in view of Bundgaard. Applicants respectfully assert that the Office has not met its burden to establish a *prima facie* case of obviousness under § 103.

In order to establish a *prima facie* case of obviousness, the Office has the burden of showing the following three criteria: 1) a suggestion or motivation to modify or combine the reference teachings; 2) a reasonable expectation of success; and 3) the teaching of all the claim limitations by the reference(s). MPEP § 2143. Applicants respectfully assert that the Office has not met its burden because Jerussi '048 and Bundgaard alone, or in combination, do not teach all of the claim limitations.

Claims 1-19 of the present invention recite compounds which are alkyloxycarbonyloxyalkyl ethers (i.e., R_1 is the alkyloxy functionality) of O-desmethylvenlafaxine, as well as pharmaceutical compositions and methods of treating of treating specified disorders utilizing this particular prodrug form. Jerussi '048 discloses the use of (-)-O-

desmethylvenlafaxine to treat various disorders in humans. Jerussi '048 does not disclose the use of any prodrug of O-desmethylvenlafaxine to treat these diseases, much less the specific prodrug of the present invention. To overcome this deficiency, the Action combines the Bundgaard reference.

Bundgaard teaches the design of various prodrugs. In particular, the Action points to pages 5-6 as indicating that acyloxyalkyl ethers can be used with phenolic drugs to create prodrugs. Bundgaard, however, does not disclose alkyloxycarbonyloxyalkyl ethers as prodrugs for phenolic drugs. Only Applicants teach this particular prodrug form. Since Jerussi '048 and Bundgaard alone, or in combination, do not teach the specific compounds of the present invention, or pharmaceutical compositions and methods of treatment thereof, Applicants respectfully assert that the Office has not established a *prima facie* case of obviousness. Accordingly, withdrawal of the rejection based on 35 U.S.C. § 103 is respectfully requested.

Minor Amendments

Applicants have also made a number of amendments to correct minor typographical errors in claims 1, 4, and 22. Applicants respectfully assert that these amendments neither narrow the claims nor introduce new matter.

Early reconsideration and allowance of all pending claims is respectfully requested. The examiner is requested to contact the undersigned attorney if an interview, telephonic or personal, would facilitate allowance of the claims.

The Commissioner is hereby authorized to charge any fee or underpayment thereof or credit any overpayment to deposit account no. 50-1275.

Respectfully submitted,
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